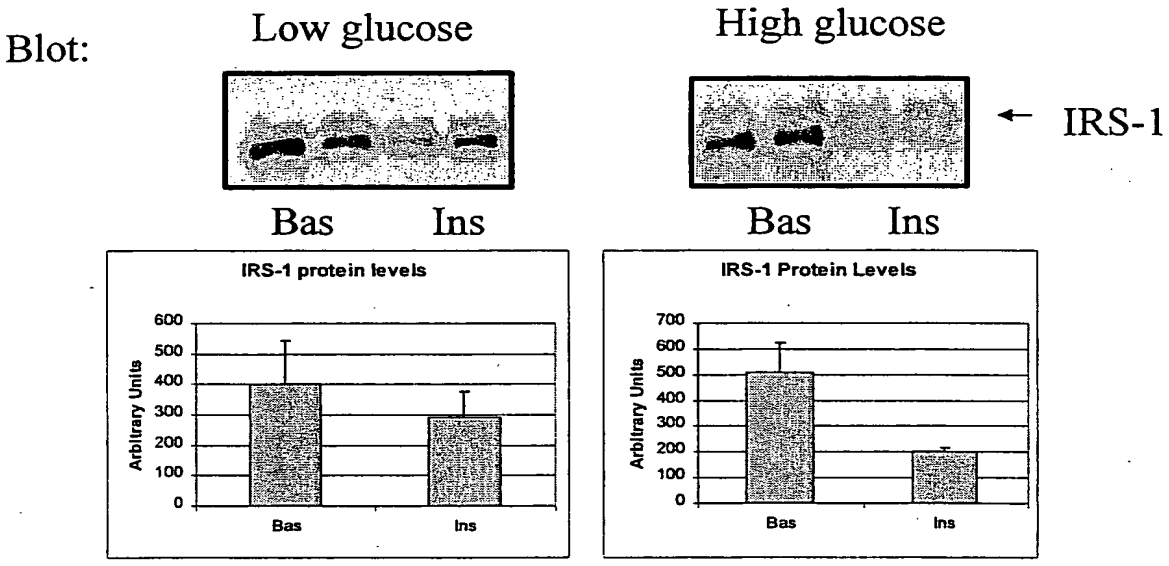

Blot:
Low glucose
High glucose
IRS-1
Bas
Ins
Bas
Ins
IRS-1 protein levels
Arbitrary Units
600
500
400
300
200
100
0
Bas
Ins
IRS-1 Protein Levels
Arbitrary Units
700
600
500
400
300
200
100
0
Bas
Ins

Figure 1


Untreated
Control Oligo
p70S6 siRNA
p70S6
β-actin
0.25 x 10⁶ cells/well TransIT-TKO
p70S6
0.50 x 10⁶ cells/well TransIT-TKO
p70S6
0.75 x 10⁶ cells/well Lipofectamine 2000

Figure 2

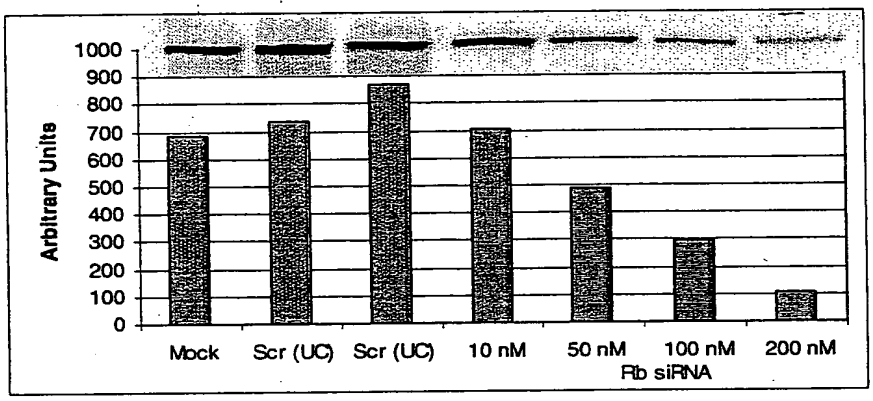

Arbitrary Units
1000
900
800
700
600
500
400
300
200
100
0
Mock
Scr (UC)
Scr (UC)
10 nM
50 nM
100 nM
200 nM
Rb siRNA

Figure 3

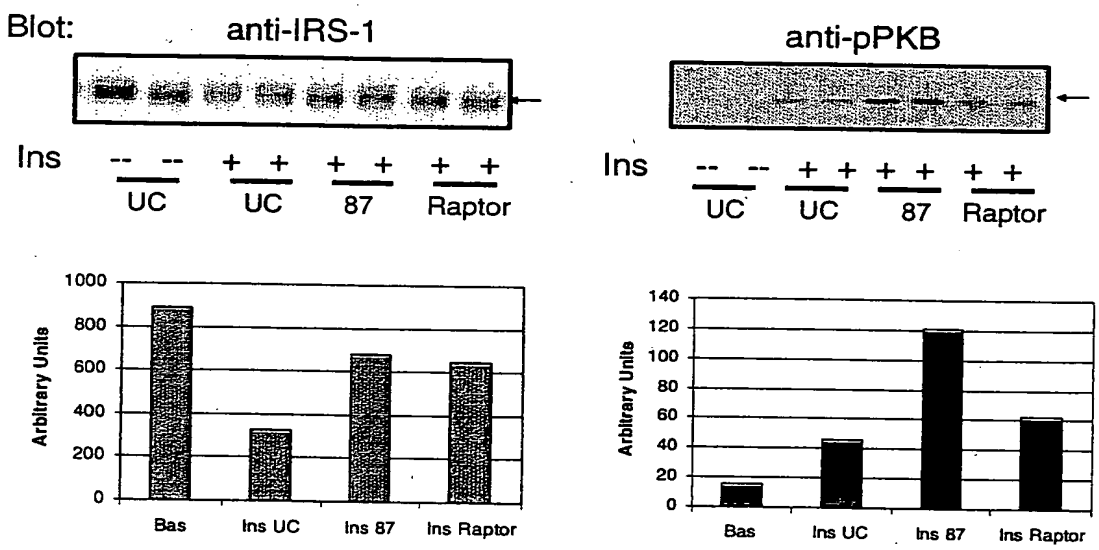

Blot:
anti-IRS-1
anti-pPKB
Ins
-- -- + + + + + +
UC UC 87 Raptor
Ins
-- -- + + + + + +
UC UC 87 Raptor
Arbitrary Units
1000
800
600
400
200
0
Bas
Ins UC
Ins 87
Ins Raptor
Arbitrary Units
140
120
100
80
60
40
20
0
Bas
Ins UC
Ins 87
Ins Raptor

Figure 4

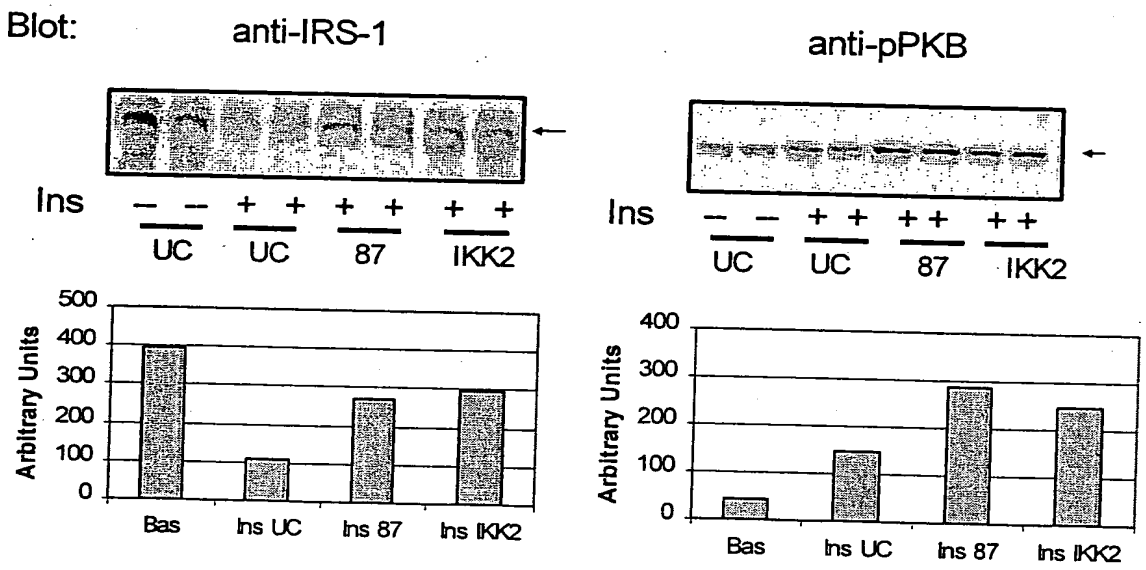

Blot:
anti-IRS-1
anti-pPKB
Ins
– – + + + + + +
UC UC 87 IKK2
Arbitrary Units
500
400
300
200
100
0
Bas
Ins UC
Ins 87
Ins IKK2
Ins
– – + + + + + +
UC UC 87 IKK2
Arbitrary Units
400
300
200
100
0
Bas
Ins UC
Ins 87
Ins IKK2

Figure 5

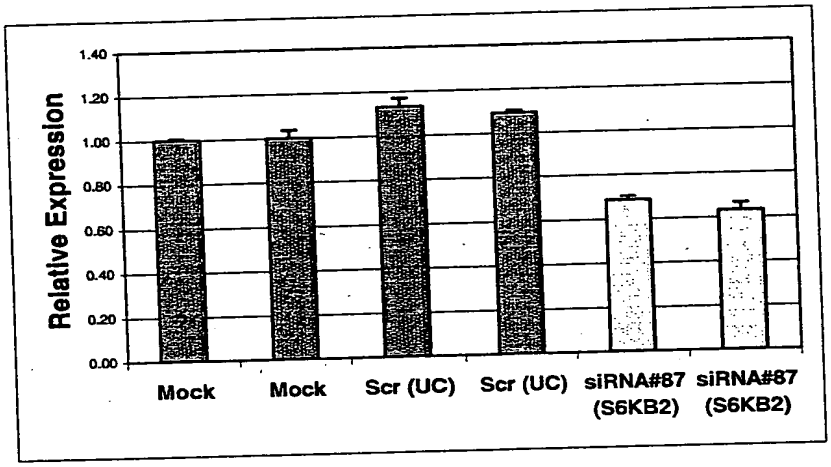

Relative Expression
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Mock
Mock
Scr (UC)
Scr (UC)
siRNA#87 (S6KB2)
siRNA#87 (S6KB2)

Figure 6

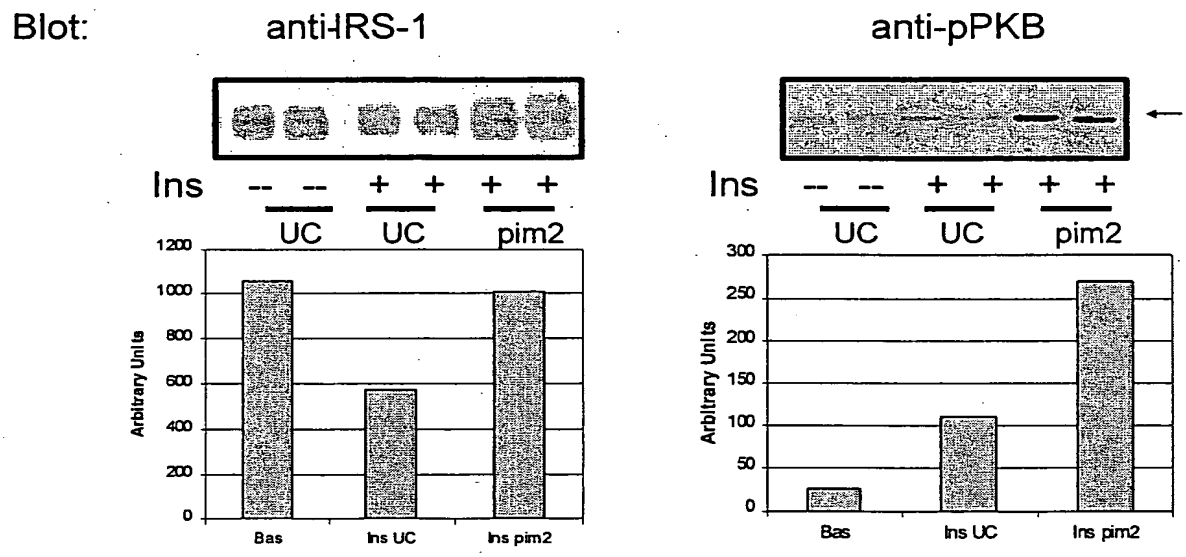

Blot:
anti-IRS-1
anti-pPKB
Ins
-- -- + + + +
UC
UC
pim2
Arbitrary Units
1200
1000
800
600
400
200
0
Bas
Ins UC
Ins pim2
300
250
200
150
100
50
0

Figure 7

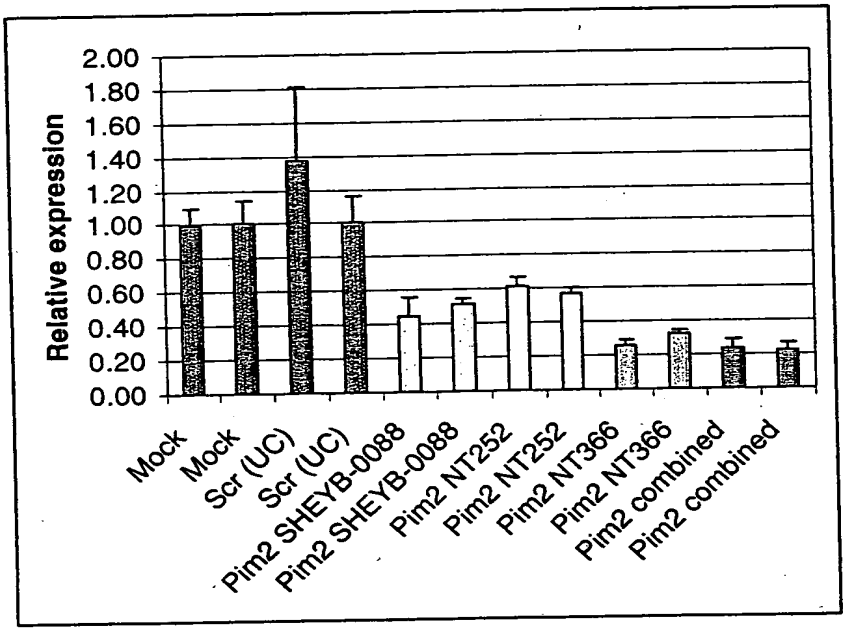
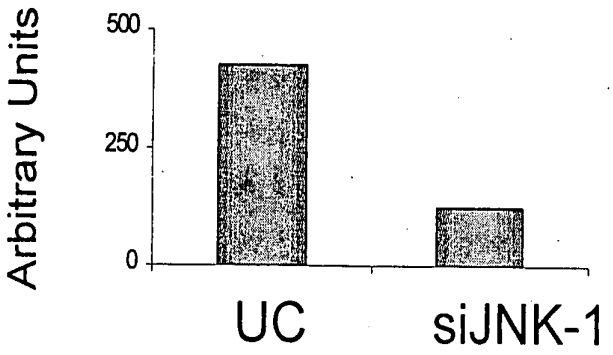

Relative expression
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
Mock
Mock
Scr (UC)
Scr (UC)
Pim2 SHEYB-0088
Pim2 SHEYB-0088
Pim2 NT252
Pim2 NT252
Pim2 NT366
Pim2 NT366
Pim2 combined
Pim2 combined

Figure 8

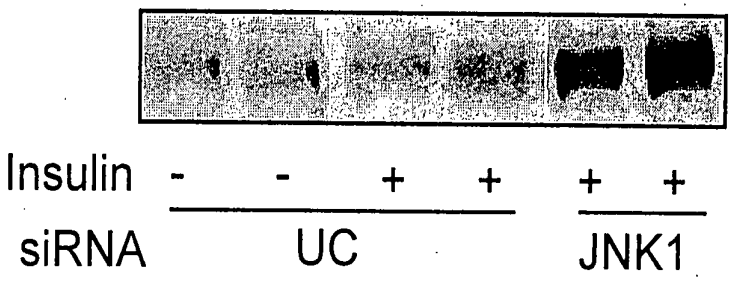
Fig. 9

Reduction of JNK-1 inhibits IRS-1 degradation and enhances insulin-induced PKB phosphorylation

JNK-1 protein expression



Anti-IRS-1



- JNK activity is elevated in Type 2 diabetes and insulin resistance states
- JNK-1 -/- are protected to the development of diet induced obesity and insulin-resistance
- Reduction of JNK-1 in ob/ob mice improves insulin sensitivity and prevents diabetes

Anti-pPKB

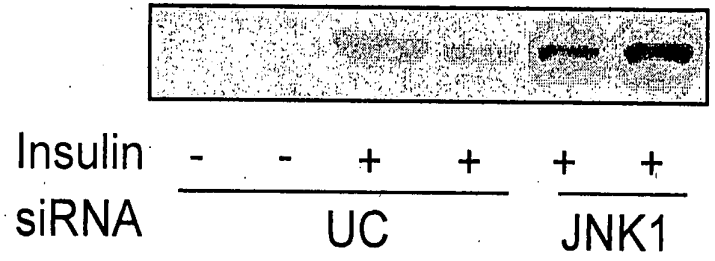
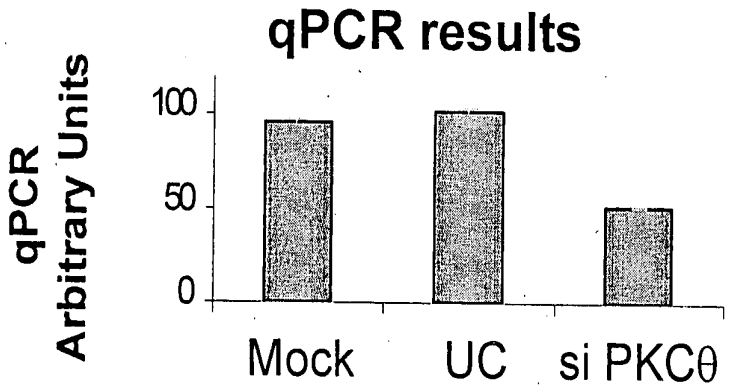
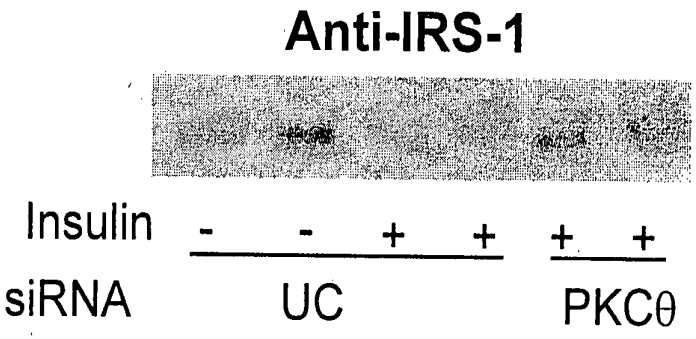


Fig. 10

Reduction of PKCθ inhibits IRS-1 degradation and enhances insulin-induced PKB phosphorylation





- FFA-induced insulin resistance is associated with activation of PKCθ
- PKCθ KO mice are protected from lipid induced insulin-resistance
- Increased PKCθ in muscle of patients with type 2 diabetes
- Chronic hyperinsulinemia increases PKCθ expression

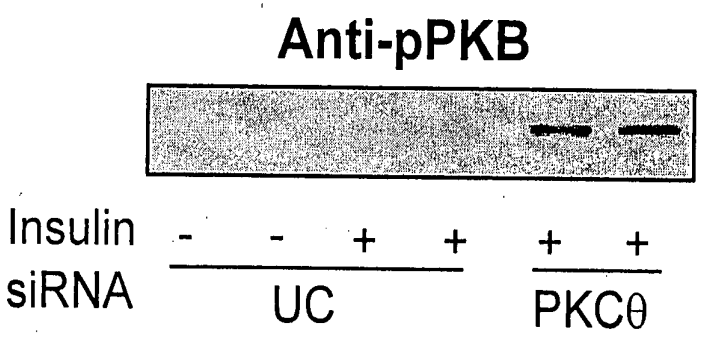
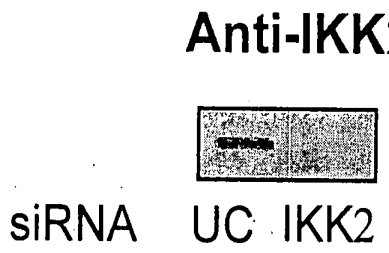
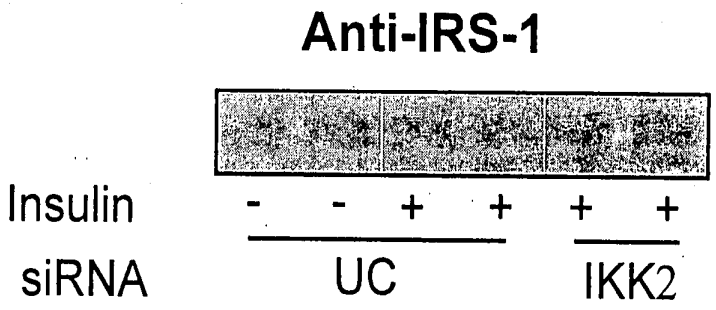


Fig. 11

Reduction of IKK2 inhibits IRS-1 degradation and enhances insulin-induced PKB phosphorylation





- Overexpression of IKK2 cause insulin resistance
- Expression of dominant negative IKK2 reverses TNF, FFA and hyperglycemia induced resistance
- IKK2 has been shown to be a target of high dose salicylates
- Heterozygous deletion (Ikkbeta+/-) protected against the development of insulin resistance during high-fat feeding and in obese (ob/ob) mice

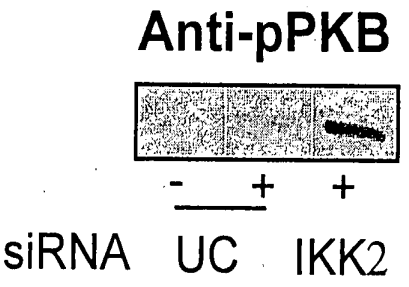
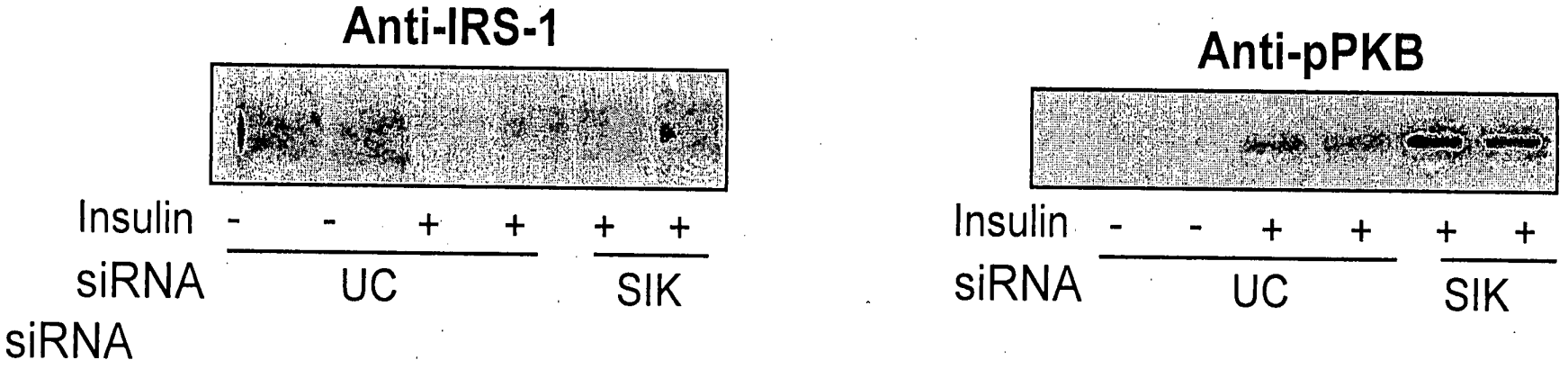


Fig. 12

Salt-inducible kinase-1 (SIK) is a new kinase involved in insulin resistance



- SIK was first cloned from the adrenal glands of rats fed a high salt diet
- Serine/threonine protein kinase that belongs to AMPK family
- SIK1 mRNA is elevated in adipose tissues, livers, and skeletal muscle of diabetic animals
- Involved in the phosphorylation of Ser^{789} in IRS-1 in livers of diabetic animals